**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service
Food and Drug Administration

# Memorandum

1858 5 JUN 30 P2:1

Date: JUN 14 2005

From: Consumer Safety Officer, Division of Dietary Supplement Programs , Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: _Bacillus subtilis DB9011__

Firm: __BAU, Inc_____

Date Received by FDA: __ March 15, 2005 ___

90-Day Date: __ June 13, 2005

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

___*Victoria Lutwak*___

19955-0316

RPT277

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

Mr. John Will Ongman,
Attorney
Barnes and Thornburg
Suite 900
750 17th St., NW
Washington DC 20006-4607

MAY 27 2005

Dear Mr. Ongman:

This is to inform you that the notification, dated March 10, 2005, you submitted on behalf of your client, BAU, Inc. pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on March 15, 2005. Your notification concerned the substance that you identified as "Bacillus subtilis DB9011" that you intend to market as a new dietary ingredient in a dietary supplement product which you call "Product #1 [Self-up]".

According to your notification, your new dietary ingredient will be marketed in capsules containing 16.5 mg of the ingredient, "Bacillus subtilis DB9011". Your notification states that the conditions of use will be to "[t]ake one to three capsules per day[.] Store capsules in a cool and dark place. Do not consume capsules after expiration date. A physician should always be consulted for your health problems and symptoms. Discontinue use of this product and immediately consult a medical professional if any adverse reaction occurs."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b (a) (2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. 342(f) (1) (B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your submission and the agency has concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing "Bacillus subtilis DB9011" will reasonably be expected to be safe.

Your notification fails to clearly identify the new dietary ingredient because the notification did not include an adequate description of the final composition of your new dietary ingredient, "Bacillus subtilis DB9011". For example, it is not clear if your ingredient is composed solely of the organism or also includes culture medium or other substances introduced during production. Furthermore, you note that you will add 13.5 mg of a substance that you call "oligosaccharide" as an excipient but do not name or characterize "oligosaccharide" in a way that allows FDA to determine that it is an ingredient appropriate for use in a dietary supplement product.

Your notification provides, as evidence of safety, history of use of *Bacillus subtilis* in foods such as natto. In attachment F, you suggest that consumers of your product will be exposed to *B. subtilis* at levels many times that which would be consumed in a serving of natto, but your notification does not provide a direct quantitative comparison of serving levels of *B subtilis* in natto and your dietary supplement product or indicate why you believe that this increased serving level is reasonably likely to be safe under the conditions of use of your product. Similarly, Attachment D describes a murine toxicity test but does not indicate whether the test substance was a bacterial culture, your new dietary ingredient, your dietary supplement product or how the test substance was quantitatively or qualitatively related to the dietary supplement product that you intend to market.

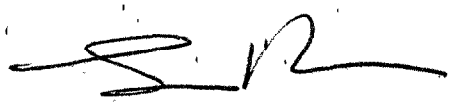
You state in your notification that "Bacillus Subtilis DB9011 has been sold in Japan and the Philippines for over a year and that no harmful effects have been reported. As evidence, you provided a copy of a registration certificate, dated January 25, 2005, from the Republic of the Philippines for a product called "DREAMY BACILLUS 9011 Natto Bacillus Food Supplement Capsules". However, your notification does not describe how the products used in the Philippines and Japan are quantitatively and qualitatively related to the dietary supplement product that you intend to market in the United States, how the conditions of use of the products marketed in the Philippines and Japan compare to those proposed for the U.S. product or how this history of use provides a basis to conclude that the product you intend to market in the U.S. will be safe under the proposed conditions of use.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that "Bacillus subtilis DB9011" when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of March 15, 2005. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter, please contact Linda S. Pellicore, Ph.D. at (301) 436-2375.

Sincerely yours,



Susan J. Walker, M.D.
Director
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ORIGINAL

March 10, 2005

Susan Walker, Ph.D.
Office of Nutritional Products, Labeling and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

Re: Premarket Notification of New Dietary Ingredient

Dear Dr. Walker:

Pursuant to 21 C.F.R. §190.6, BAU Inc. submits an original and two copies of this premarket notification of its intent to distribute a dietary supplement that contains a new dietary ingredient -- namely Bacillus subtilis DB9011.

1. **Name and Complete Address of Manufacturer or Distributor of Dietary Supplement or of the New Dietary Ingredient**

Manufacturer of Bacillus subtitlis DB9011 and Other Ingredients in Dietary Supplement

AHC Co. Ltd.
Koaigi-machi 343-1
Maebashi
Gunma 371-0831
Japan

Manufacturer of Packaging

MDF Co. Ltd.
Miyashita 272-1
Fujinimiya
Shizuoka 416-0947
Japan

Distributors of Dietary Supplement including New Dietary Ingredient

Bio and medical infromatics Inc.
4-9-3
Shiba
Minato-Ku
Tokyo 108-0014
Japan

BAU, Inc.
(Bio and medical informatics & AHC, USA)
1840 Oak Avenue
Suite 116
Evanston, Illinois 60201

2. **Name of the new dietary ingredient**

Bacillus subtilis DB9011. This new dietary ingredient is patented in the United States. See **Pure Culture of *Bacillus Subtilis* FERM BP-3418**, US Patent 5,364,788 issued November 15, 1994. A copy of this patent is attached hereto as Attachment A. The corresponding European Patent -- **Novel bacillus bacterium and its usage**, EP 0 537 418 B1 -- was published on May 13, 1998 and designated application in Austria, Germany, Denmark, France, Great Britain, Italy, and the Netherlands. A copy of this patent is attached hereto as Attachment B. The Japanese version of this patent bears the Japanese patent number 3040234.

Bacillus subtilis DB9011 was separated from the soil in 1990 by AHC Co. Ltd, the patent holder. AHC Co. Ltd is a parent company of BAU, Inc. Bacillus subtilis DB901, is of the genus Bacillis subtilis, and is a relative of Bacillus subtilis natto. Bacillus subtilis DB9011 was deposited on May 21, 1991 under Fermentation Research Institute Accession Number 3418 (FERM BP-3418) at the National Institute of Bioscience and Human Technology, Agency of Industrial Science and Technology, Japan Ministry of International Trade and Industry (former Fermentation Research Institute) in accordance with the Budapest protocol.

3. **Description of dietary supplement that contains the new dietary ingredient**

a. **Level of new dietary ingredient in dietary supplement**

16.5 mg of Bacillus subtilis DB9011 in a 360 mg capsule (13.5 mg of the 30mg assigned to the Bacillus subtilis DB9011 is oligosaccharide used as an excipient). See Product Composition chart attached hereto as Attachment C.

b. **Conditions of use**

Take one to three capsules per day

Store capsules in a cool and dark place.

Do not consume capsules after expiration date.

A physician should always be consulted for your health problems and symptoms. Discontinue use of this product and immediately consult a medical professional if any adverse reaction occurs.

4. **History of use or other evidence of safety**

Generally, the genus Bacillus subtilis is known as safe for humans. For example, Bacillus subtilis natto is present in natto, a fermented soybean foodstuff which has been a staple of the traditional Japanese diet.

As to Bacillis subtillis DB9011, there is also specific evidence of safety. First, the safety of this bacterium for animal consumption was established in December 1995 by the Tokyo Food Sanitation Association of the Tokyo District Food Institute of Technology. This Association is a non-profit food safety organization which is authorized by the Japanese government to make food safety tests for the food industry. The Association performed on mice an acute toxicity test, an ocular-mucous membrane spot stimuli test, and a skin stimuli test. The results of the Association's test are set forth in Attachment D hereto.

Second, a dietary supplement using Bacillus subtillis DB9011 has been sold in Japan and the Phillipines for more than one year and no harmful effects have been reported. No certification procedure was required to introduce the dietary supplement in Japan since Bacillis subtillis natto has long been a staple of the traditional diet in Japan. The certification from the Phillipines is attached hereto as Attachment E.

Third, Bacillus subtillis DB9011 has been introductive into livestock foodstuffs in Japan for over 10 years with no harmful effects on the livestock.

Presentations and articles have confirmed these conclusions. We include the following materials. Please note that (notwithstanding certain subjects discussed in these materials) BAU Inc. intends only to make permitted structure/function statements and not to make disease claims:

a. "Old and New Discovery of Bacterium with Strong Immunity Activating Power and Its Applications," Presentation dated February 22, 2005 of Mr. Masashi Kito, President of BMI, a parent company of BAU Inc. to the Highly Advanced Medical Technology Study Group. Attachment F hereto. This Group is one of the most prestigious medical organizations in Japan.

b. Masashi Kito, "Life Force Bacillus" published in the November 2004 issue of the personal health magazine Hatsuratsu genki. Attachment G hereto. Mr. Kito is

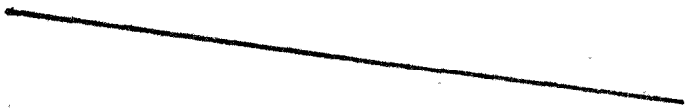
President of both BMI and BAU and is currently a guest researcher on Bacillus subtillis DB9011 at Waseda University in Japan. The chart in the article on NK cell production was based on an animal test done by Nihon University in 2004. The human efficacy data was based on a questionnaire collected in 2004 by the Phillipines office of the manufacturer and distributor and sent to Pilipino consumers..

c. Hiroiku Ueno, "DB 9011, from the bacillus subtillis group, boosts your immune system, helping speed the recovery period after cancer treatment and surgery, and can help prevent cancer recurrence" published in the February 2005 issue of the monthly magazine Gan (Cancer). Attachment H hereto. This is a medical magazine for cancer patients and their families. Dr. Ueno is a Ph.D., a director of Asahi Iou Clinic, a guest professor of Niigata University of Pharmacy and Applied Science, and a director of the Japanese Clinical and Alternative Medicine Medical Society.

d. Jun Ishikawa, "Immune Activation Effects of DB-9011 on Dogs and Cats" (October 3, 1996). Attachment I hereto. Dr. Ishikawa is at the Obihiro University of Agriculture and Veterinary Medicine.

e. Yoko Hrano et al., "Preventative Effect of Treatment of Bacillus Subtilis DB-9011 on Dogs of which Cellular Immune Function is Decreased by Surgical Operation" (October 30, 1996). Attachment J hereto. The authors are at the College of Bioresource Science of Nihon University.

f. 

g. 

h. Yoshiya Asano et al., "Establishment of Monoclonal Antibodies Specific for Bacillus subtilis DB9011," Biosci. Biotechnol. Biochem., 64(3), 652-656 (2000). Attachment M hereto. These researchers are at Gunma University. The study was completed on November 26, 1999.

5. **Signature of person designated by the manufacturer or distributor**

The person designated by the distributor BAU, Inc. is:

Jin Hashimoto
BAU, Inc.
(Bio and medical informatics & AHC, USA)
1840 Oak Avenue
Suite 116
Evanston, Illinois 60201
Telephone (847) 866-1848
Fax (847) 866-1808

Mr. Hashimoto's signature is affixed to the Signature Page attached hereto as Attachment N hereto.

* * *

Should you require any further information or have any questions on this premarket notification, please contact me directly so that I may convey any inquiry from the FDA in a manner to ensure that it is properly understood by BAU, Inc. and its Japanese affiliates.

Very truly yours,

John Will Ongman

Enclosures